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Methamphetamine Addiction: A Review of the Literature

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Abstract

Methamphetamine, a synthetically produced central nervous system stimulant, is the second most illicit drug worldwide after cannabis. This drug has an annual global prevalence estimated at 0.4%, and its use is important in North America, Asia, and Oceania.

Literature review was conducted from 1989 to 2011, using PubMed, Google Scholar, EMBASE, and PsycInfo, using the following key words alone or in combination: methamphetamine, addiction, dependence, complications, and pharmacotherapy.

Methamphetamine addiction is a serious public health problem with many consequences and complications. Significant morbidity, including cardiovascular, infectious, pulmonary, dental diseases and other systems complications are associated with methamphetamine acute or chronic use. Methamphetamine dependence also causes serious cognitive impairments that can persist during abstinence and negatively affect recovery outcomes.

There are no approved medications for the treatment of methamphetamine dependence. Efficient treatments include behavioural and psychological approaches of contingency management, cognitive-behavioural therapy, and motivational enhancement strategies.

Introduction

Methamphetamine is a synthetically produced central nervous system stimulant [1]. This drug is the second illicit drug used after cannabis in North America Asia, and Oceania, with an annual global prevalence estimated at 0.4% [1]. Its use remains marginal in Europe except in the Czech Republic (2,8 cases for 1000) and Slovakia (1,5 to 4 cases for 1000) [2]. This drug is usually sold in powder, paste or crystal form. Routes of administration are intranasal sniffing, oral ingestion, pulmonary inhalation, and injection [3]. The effects of methamphetamine use include subjective euphoria, arousal and psychomotor activation [3].

Methamphetamine also known under the street names of "speed", "ice", "crystal", "glass" "meth" or "kryptonite". Dependence is a serious worldwide public health problem associated with major medical, psychiatric, cognitive, socioeconomic and legal consequences. Physiological dependence associated withdrawal-related symptoms and craving are thought to reinforce continued drug-taking, including methamphetamine self-administration [4-6]. If effective public health responses to methamphetamine use are to be implemented, an understanding of the specific harms associated with methamphetamine is necessary. Currently, there is no pharmacological therapy with established efficiency for the treatment of this addictive disorder, and no medications proven to be effective in treating this disorder [7-8].

Literature review was conducted from 1989 to 2011, using PubMed, Google Scholar, EMBASE, and PsycInfo, using the following key words alone or combined: methamphetamine, addiction, dependence, complications, and pharmacotherapy.

Epidemiology

The 2009 World Drug report suggests that up to 51 million individuals (1.2% of the global population aged 15-64 years) have used methamphetamine at least once in the past 12 months [9]. In the United States, data from the 2007 National Survey on Drug Use and Health (NSDUH) indicates that 0.1% of 12-17-years-olds and 0.4% of 18-25-years-olds reported using Methamphetamine in the past month, representing more than 150,000 young users in the United States [10]. While the prevalence of methamphetamine use in the general population is low, rates in younger age groups are significantly higher [11], and life time use of methamphetamine is higher among men than women [11,12]. Methamphetamine use has gained high levels of attention among gay and bisexual men substances users in urban areas [11,12]. In a probability-based survey, approximately 11% of gay and bisexual men in Los Angeles and 13% in San Francisco reported using the drug in the previous 6 months [13]. The popularity of Methamphetamine stems partly from its availability and reasonably low cost, and from disinhibiting effects linked to sexual behaviours [13].

Clinical Pharmacology

Manufacture

Methamphetamine is produced through reduction of ephedrine or pseudoephedrine [14]. Methamphetamine is often mixed with other substances, including caffeine or talc. There are two isomeric forms of methamphetamine, d-amphetamine and l-methamphetamine. The d-isomer is more potent and is the form manufactured for illicit use. The d-isomer form is 80-90% pure [14].

Methamphetamine

Methamphetamine is available in different forms such as a pure crystalline hydrochloride salt or as formulated tablets. Routes of administration are intranasal sniffing, pulmonary inhalation, injection and oral ingestion [14].

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Clinical effects

By its sympathomimetic action-like, methamphetamine accelerates heart rate, raises blood pressure and temperature, and pupil dilatation [14]. Acute methamphetamine use increases positive subjective effects and mood. It removes tiredness and brings a feeling of power, euphoria and self-control [14,15]. Subjective and cardiovascular effects appear to increase depending on the dose. [15].

Withdrawal symptoms

Withdrawal symptoms have been linked to a propensity for a relapse of drug abuse. Dysphoric mood is the main symptom for methamphetamine withdrawal, which requires at least two of the following additional symptoms to establish a diagnostic: psychomotor agitation or retardation, vivid, unpleasant dreams, fatigue, insomnia or hypersomnia, and increased appetite [16,17]. Depressive symptoms vary considerably in intensity and duration, and resolve during the first two weeks of abstinence [18]. Less severe symptoms of withdrawal include anxiety, motor retardation, agitation, vivids dreams, poor concentration, irritability and tension decrease at the end of the first week of abstinence (7-10 days) [19].

The severity of Methamphetamine withdrawal symptomatology, which varies among individuals [20], is likely to influence the ability of MA-dependent patients to maintain abstinence [18].

An understanding of methamphetamine withdrawal may inform on the development of strategies for relapse prevention.

Psychiatric, addictive complications and consequences

Methamphetamine use is associated with a substantial burden of psychopathology, which includes elevated rates of psychosis, mood and anxiety disorders, violent behaviours and cognitive deficits.

Psychosis

Psychosis induced by methamphetamine is a typically transient phenomenon that involves symptoms of delusions, and hallucinations [14]. Methamphetamine-induced hallucinations are predominantly auditory (experienced in 85% of cases of methamphetamine psychosis), visual (46%) and tactile (21%). Delusion of persecution (71%), of reference (63%) and of "mind reading" (40%) are also common [14-21]. There is considerable variability in both the dose required and the onset of psychotic symptoms (7 minutes-34 minutes) [14]. The duration of psychotic symptoms is variable, dissipating within a week of abstinence, or persisting indefinitely [14]. Psychosis can also be accompanied by an emotionally labile state, agitation and hostile behaviour, and can require hospitalisation sedation and antipsychotic medication in severe cases [22]. Psychosis induced by methamphetamine is a transient phenomena remitting rapidly following the stop of consumption [23]. Although vulnerability to psychotic symptoms varies among users, a research reported that 23% had experienced a clinically significant psychotic symptom in the past year and 13% screened positive for a psychotic disorder (compared with 1.2% of the general population) [24].

A number of factors have been associated with an increased risk of developing psychotic symptoms. They are most likely to occur among chronic and dependent users of the drug [24-26]; a study showed that 31% of dependent methamphetamine users had psychotic symptoms, compared with 13% of non-dependent-users [24]. Longer periods of use [23-25], heavier use [24,25], the way of administration (injection) [14], and a pre-existing history of psychotic symptoms increases [21] the risk of psychotic symptoms induced.

Methamphetamine use can precipitate and exacerbate psychotic symptoms among people suffering from schizophrenia [23]. Therefore, Methamphetamine users who have a pre-existing proneness to psychosis are at particularly high risk of experiencing symptoms of psychosis [23].

Depression

Depressive symptoms are common [27]. A recent study reported that a third of methamphetamine users had been diagnosed with depression at some point in their lives [27]. A recent prospective cohort study of young Thai methamphetamine-users found that depressive symptoms decreased significantly among those who stopped using methamphetamine over the 12-month study period [28]. Methamphetamine initiation during adolescence is associated with adulthood depression, whereas early depression was not predictive of future Meth use [29,30]

Anxiety

High levels of anxiety disorders are reported [25,31,32]. Half of methamphetamine users reported symptoms of anxiety prior to initiation, and 75% had experienced severe anxiety symptoms since methamphetamine use [22]. 11% of methamphetamine users have received a diagnosis of an anxiety disorder in their lives [27].

Higher levels of depression, suicide and anxiety have been associated with longer methamphetamine use, early onset, high degree of dependence, frequent use and injecting [24,25,32,33].

Violent behaviours

Violent behaviours appear common among methamphetamine users, particularly among people who inject these drugs [24,25,27], and after methamphetamine use [14]. In the McKetin et al. study, 12% of methamphetamine users had committed a violent crime in the preceding year [27]. Sommers and al. found that more than a third of methamphetamine users had assaulted someone while intoxicated with the drug [33].

Addictive comorbidities

Methamphetamine users consume a variety of drugs. Cannabis use is common, and the majority drinks alcohol. Some have a history of heroin use, and the use of other psychostimulants is common [27-34]. The importance of concomitant use of other substances with methamphetamine is that, when combined with alcohol, cocaine or opiates, methamphetamine toxicity is increased [35,36].

Overdose

Overdose appears to be significant sources of morbidity and mortality among young methamphetamine users [37], and includes agitation, dilated pupils, hypertension, tachycardia, and rapid respiration [14]. Other features include hyperthermia, shivering, dyspnee, chest pain, renal failure, and coma [14]. Elevated risks of overdose among non-injecting methamphetamine users are reported [38]. Those who inject methamphetamine either on its own or in combination with other illicit drugs such as heroin are also at risk of suicide [38,39].

Health Outcomes Associated with Methamphetamine Use

Cardiovascular pathologies

Methamphetamine users are at an elevated risk of cardiac

pathology. Emergency department data has shown consistent chest pain, cardiac arrhythmias (tachycardia), palpitations and hypertension to be among the most common physical symptoms after methamphetamine intoxication [42-45]. A prolongation of the QTc beyond 440 ms is reported among 27.2% of the methamphetamine users [46]. Cardiovascular consequences of methamphetamine use include acute coronary syndrome, acute myocardial infarction, acute aortic dissection, and sudden cardiac death [47]. Cardiovascular complications associated with methamphetamine use can occur with all of the major routes of administration [47].

When methamphetamine is combined with alcohol, cocaine or opioids, toxicity and stress on the cardiovascular system is increased [48].

Cerebrovascular complications

Methamphetamine use is associated with ischemic stroke, intracerebral haemorrhage and subarachnoid haemorrhage, especially among young patients [49]. A study showed no evidence that the ischemic stroke associated with methamphetamine use is due to an inflammatory etiology but may be due to a process of accelerated atherosclerosis [49]. Methamphetamine leads to increased catecholamine levels, leading to coronary vasoconstriction, production of oxygen-free radicals, myocardial fibrosis, and cardiomyopathie because of the direct toxicity to extra and intracerebral vessels, leading to changes in luminal calibre [49].

Neurotoxicity

Repeated use of methamphetamine involves the degeneration of dopamine and serotonin axons and termini, located in the fronstostrial region, leading to depletion of these monoamines [50,51]. The mechanisms of neurotoxicity are not understood completely, but involve oxidative stress and apoptosis [52-54]. Primate experiments demonstrate that methamphetamine use can lead to neurotoxicity that may require more than a year for complete recovery. *In vivo* human positron emission tomography and magnetic resonance imaging showed brain abnormalities including inflammation [55], reduced neuronal density [55] and reduced density of dopaminergic markers [56-58]. These abnormalities mediate cognitive deficits among methamphetamine users, caused by damages in the cingulated, frontal, and striatal regions [59,60].

Parkinson's disease

Parkinson's disease psychomotor disturbances have been reported among methamphetamine heavy users [61]. To confirm this hypothesis, a retrospective case-controlled study revealed that prolonged use of methamphetamine is associated with an eight-fold increased risk of Parkinson's disease with an average of 27 years between amphetamine exposure and the onset of signs [62].

Neuropschological impairment

Neurocognitive impairment caused by methamphetamine is caused by frontostrial and limbic abnormalities. The main functions altered are learning, episodic memory, executive functions, speed of information treatment, working memory and perceptual narrowing [63]. The cognitive deficits persist over six months after withdrawal [64,65].

Sexual behaviours

Methamphetamine use is reported to enhance sexual pleasure, to facilitate prolonged sexual activity, and to delay and increase orgasm [66,67].

Methamphetamine is used in combination with drugs such as sidenafil to enhance sexual performance [67,68]. The association with others drugs (cocaine, rohypnol) promotes compulsive sexual activity and high-risk activities such as unprotected, anonymous and receptive anal sex among homosexual methamphetamine dependent users [69-72].

Infectious diseases and blood borne virus transmission

Sexual risk behaviour and sharing used needles increase the risk of blood-borne virus transmission (HIV, hepatitis B, hepatitis C) [14]. Methamphetamine-using homosexual men are a high-risk group for HIV seroconversion, because of the high use of methamphetamine among homosexual men who engage in risky sexual practices and those with HIV [73,74]. A study has shown a significantly increased risk of Chlamydia trachomatis infection among methamphetamine-using women [75].

Other outcomes

Studies showed a strong association between methamphetamine use and dental diseases, with a greater number of decayed, missing or extracted teeth among methamphetamine users compared to controls [76]. Others studies reported that teeth grinding [77] and jaw pain [77] and "*meth mouth*"[DDDDD] were more common among the group of methamphetamine users. "*Meth mouth*" is a term used to describe the mouth of a methamphetamine user because of the rampant tooth decay that often occurs with the use of this dangerous drug [78]. Using meth can cause decay so badly that the teeth cannot be saved and must be pulled out instead. Several mechanisms have been proposed (Methamphetamine-induced xerostomia, increased consumption of soft drinks, reduced behaviours) [79], although it is noteworthy that all causal pathways remain hypothetical [80].

Other causes of death

Pulmonary oedema, pulmonary congestion, cerebrovascular haemorrhage, ventricular fibrillation, acute cardiac failure or hyperpyrexia are the main causes of death [14]. Other leading causes of death are related with septic injection or asphyxia by aspiration of vomitus [14].

Pharmacological approaches

Recent improvements in the understanding of the underlying neurobiology of methamphetamine dependence have led to the emergence of promising targets. The adopted strategy has to a large extent resembled the approach to research on cocaine dependence pharmacotherapy, and employed similar preclinical and clinical models [SS]. No substantial evidence for efficient treatment has yet emerged [81]. Clinical trials using aripiprazole [82,83], GABA agents (gabapentin [84,85], baclofen [84], vigabatrin [86,87]), SSRIs [88-90], ondansetron [91,92] and mirtazapine [48-93] have failed to show efficacy [81]. In a double –blind, placebo-controlled design, naltrexon 50 significantly decreased the subjective effects produced by drugs in dependent patients [94]. Trials involving bupropion [8,95,96] and modafinil [97,98] have demonstrated possible benefits in treating methamphetamine use in dependent patients.

The PROMETA protocol, consisting of flumazenil, gabapentin and hydroxyzine, was tested to treat methamphetamine dependence. It appears to be no more than a placebo in reducing methamphetamine use, retaining patients in treatment or reducing methamphetamine craving [99].

Immunotherapies, an innovative treatment strategy of drug

addiction, may be effective in blocking the effects of drug abuse [100]. Preclinical studies have shown the therapeutic potential of the anti-methamphetamine monoclonal antibodies (AMMA) approach [101-103]. Reduction of methamphetamine self-administration, locomotor activity and inhibition of discriminative stimulus effects of methamphetamine was shown in rats and pigeons [104-106]. The two primary indications for the use of AMMA in the treatment of human methamphetamine dependence would be overdose and relapse prevention [107,108].

Conclusion

Methamphetamine is the most abused illicit drug world-wide after cannabis, with about 15-16 million regular users. Methamphetamine addiction is a serious worldwide public health problem with many consequences and complications. Significant morbidity, including cardiovascular, infectious, pulmonary, dental diseases and other systems complications are associated with methamphetamine acute or chronic use. Cognitive disorders, psychotic and mood disorders have been reported. Recent improvements in the understanding of the underlying neurobiology of methamphetamine dependence have led to a number of potentially useful pharmacological agents. There are no approved medications for the treatment of methamphetamine dependence. Efficient treatments include behavioural and psychological approaches of contingency management, cognitive-behavioural therapy, motivational enhancement strategies, and 12-Step programmes [109].

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